

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of the claims:

1. (Withdrawn) A mutein recombinant tissue protective cytokine lacking at least one activity selected from the group consisting of increasing hematocrit, vasoactive action, hyperactivating platelets, pro-coagulant activities and increasing production of thrombocytes, the cytokine comprising at least one responsive cellular protective activity selected from the group consisting of protecting, maintaining, enhancing or restoring the function or viability of a responsive mammalian cell, tissue or organ.
2. (Withdrawn) The recombinant tissue protective cytokine of claim 1, comprising one or more altered amino acid residue between position 11 to 15 of SEQ ID NO:10 [SEQ ID NO:1], position 44 to 51 of SEQ ID NO 10 [SEQ ID NO:2], position 100-108 of SEQ ID NO [SEQ ID NO:3], or position 146-151 of SEQ ID NO 10 [SEQ ID NO:4].
3. (Withdrawn) The recombinant tissue protective cytokine of claim 1, comprising an altered amino acid residue at one or more of the following positions of SEQ ID NO: 10: 7, 20, 21, 29, 33, 38, 42, 59, 63, 67, 70, 83, 96, 126, 142, 143, 152, 153, 155, 156, or 161.
4. (Withdrawn) The recombinant tissue protective cytokine of claim 1, comprising the amino acid sequence of SEQ ID NO: 10 with one or more of the amino acid residue substitutions of SEQ ID NOs: 15-105 and 119.
5. (Withdrawn) The recombinant tissue protective cytokine of claim 1, comprising the amino acid sequence of SEQ ID NO: 10 with a deletion of amino acid residues 44-49 of SEQ ID NO: 10.

6. (Withdrawn) The recombinant tissue protective cytokine of claim 1, comprising, the amino acid sequence of SEQ ID NO: 10 with at least one of the following amino acid residue substitutions of SEQ ID NOs: 106-118.
7. (Withdrawn) The recombinant tissue protective cytokine of any one of claims 1, 2, 3, 4, 5, or 6, further comprising a chemical modification of one or more amino acids.
8. (Withdrawn) The recombinant tissue protective cytokine of claim 7, wherein the chemical modification comprises altering the charge of the recombinant tissue protective cytokine.
9. (Withdrawn) The recombinant tissue protective cytokine of claim 8, wherein a positive or negative charge is chemically added to an amino acid residue where a charged amino acid residue is modified to an uncharged residue.
10. (Withdrawn) The recombinant tissue protective cytokine of any one of claims 1, 2, 3, 4, 5, or 6, wherein said cytokine is a human erythropoietin mutein.
11. (Withdrawn) The recombinant tissue protective cytokine of any one of claims 1, 2, 3, 4, 5, or 6, wherein said cytokine is a human phenylglyoxal erythropoietin mutein.
12. (Withdrawn) The recombinant tissue protective cytokine of any one of claims 1, 2, 3, 4, 5, or 6, wherein the responsive mammalian cell comprises a neuronal, muscle, heart, lung, liver, kidney, small intestine, adrenal cortex, adrenal medulla, capillary, endothelial, testis, ovary, endometrial, or stem cell.
13. (Withdrawn) The recombinant tissue protective cytokine responsive mammalian cell of any one of claims 1, 2, 3, 4, 5, or 6, comprising a photoreceptor, ganglion, bipolar, horizontal, amacrine, Mueller, myocardium, pace maker, sinoatrial node, sinus node, atrioventricular node, bundle of His, hepatocyte, stellate, Kupffer, mesangial, goblet, intestinal gland, enteral endocrine, glomerulosa, fasciculate, reticularis, chromaffin, pericyte,

Leydig, Sertoli, sperm, Graffian follicles, primordial follicles, endometrial stroma, and endometrial cell.

14. (Withdrawn) The recombinant tissue protective cytokine of any one of claims 1, 2, 3, 4, 5, or 6, wherein said cytokine is capable of traversing an endothelial cell barrier.

15. (Withdrawn) The recombinant tissue protective cytokine of claim 14, wherein the endothelial cell barrier comprises the blood-brain barrier, the blood-eye barrier, the blood testes barrier, the blood-ovary barrier, and the blood-uterus barrier.

16. (Withdrawn) The recombinant tissue protective cytokine of any one of claims 1, 2, 3, 4, 5, or 6, wherein said cytokine is selected from the group consisting of:

- i. a cytokine having a reduced number or no sialic acid moieties;
- ii. a cytokine having a reduced number or no N-linked or O-linked carbohydrates;
- iii. a cytokine having at least a reduced carbohydrate content by virtue of treatment of native cytokine with at least one glycosidase;
- iv. a cytokine having at least one or more oxidized carbohydrates;
- v. a cytokine having at least one or more oxidized carbohydrates and is chemically reduced;
- vi. a cytokine having at least one or more modified arginine residues;
- vii. a cytokine having at least one or more modified lysine residues or a modification of the N-terminal amino group of a cytokine molecule;
- viii. a cytokine having at least a modified tyrosine residue;
- ix. a cytokine having at least a modified aspartic acid or glutamic acid residue;
- x. a cytokine having at a modified tryptophan residue;
- xi. a cytokine having at least one amino acid group removed;
- xii. a cytokine having at least one opening of at least one of the cystine linkages in the cytokine molecule;
- xiii. a truncated cytokine;
- xiv. a cytokine having at least one polyethylene glycol molecule attached;
- xv. a cytokine having at least one fatty acid attached;

xvi. a cytokine having a non-mammalian glycosylation pattern by virtue of the expression of a recombinant cytokine in non-mammalian cells; and

xvi. a cytokine having at least one histidine tagged amino acid to facilitate purification.

17. (Withdrawn) The recombinant tissue protective cytokine of claim 16 wherein said cytokine is an asialoerythropoietin.

18. (Withdrawn) The recombinant tissue protective cytokine of claim 17, wherein said asialoerythropoietin is human asialoerythropoietin.

19. (Withdrawn) The recombinant tissue protective cytokine of claim 16, wherein said cytokine is hyposialylated or hypersialylated.

20. (Withdrawn) The recombinant tissue protective cytokine of claim 16, wherein said cytokine comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 sialic acid moieties.

21. (Withdrawn) The recombinant tissue protective cytokine of claim 16, wherein said cytokine comprises more than the fourteen sialic acid moieties present in native erythropoietin.

22. (Withdrawn) The recombinant tissue protective cytokine of claim 16, wherein said cytokine is an erythropoietin with no N-linked carbohydrates.

23. (Withdrawn) The recombinant tissue protective cytokine of claim 22, wherein said cytokine is an erythropoietin with no O-linked carbohydrates.

24. (Withdrawn) The recombinant tissue protective cytokine of claim 16, wherein said cytokine is treated with at least one glycosidase.

25. (Withdrawn) The recombinant tissue protective cytokine of claim 16, wherein said cytokine is periodate-oxidized erythropoietin.

26. (Withdrawn) The recombinant tissue protective cytokine of claim 25, wherein said periodate-oxidized erythropoietin is chemically reduced with sodium cyanoborohydride.
27. (Withdrawn) The recombinant tissue protective cytokine of claim 16, wherein said cytokine comprises an R-glyoxal moiety on the one or more arginine residues, wherein R is aryl or alkyl moiety.
28. (Withdrawn) The recombinant tissue protective cytokine of claim 27, wherein said cytokine is phenylglyoxal-erythropoietin.
29. (Withdrawn) The recombinant tissue protective cytokine of claim 16, wherein said cytokine is an erythropoietin in which an arginine residue is modified by reaction with a vicinal diketone selected from the group consisting of 2,3-butanedione and cyclohexanedione.
30. (Withdrawn) The recombinant tissue protective cytokine of claim 16, wherein said cytokine is an erythropoietin in which an arginine residue is reacted with 3-deoxyglucosone.
31. (Withdrawn) The recombinant tissue protective cytokine of claim 16, wherein said cytokine is a molecule having at least one biotinylated lysine or N-terminal amino group.
32. (Withdrawn) The recombinant tissue protective cytokine of claim 16, wherein said cytokine is a glucitolyl lysine erythropoietin or fructosyl lysine erythropoietin.
33. (Withdrawn) The recombinant tissue protective cytokine of claim 16, wherein said cytokine comprises at least one carbamylated lysine residue.
34. (Withdrawn) The recombinant tissue protective cytokine of claim 33, wherein said carbamylated cytokine is comprised of alpha-N-carbamoylerythropoietin; N-epsilon-carbamoylerythropoietin; alpha-N-carbamoyl, N-epsilon-carbamoylerythropoietin; alpha-N-carbamoylasialoerythropoietin; N-epsilon-carbamoylasialoerythropoietin; alpha-N-carbamoyl, N-epsilon-carbamoylasialoerythropoietin; alpha-N-

carbamoylhyposialoerythropoietin; N-epsilon-carbamoylhyposialoerythropoietin; and alpha-N-carbamoyl, N-epsilon-carbamoylhyposialoerythropoietin.

35. (Withdrawn) The recombinant tissue protective cytokine of claim 16, wherein said cytokine comprises at least one acylated lysine residue.

36. (Withdrawn) The recombinant tissue protective cytokine of claim 35, wherein said cytokine comprises at least one acylated lysine residue.

37. (Withdrawn) The recombinant tissue protective cytokine of claim 36, wherein said cytokine comprises at least one acylated lysine residue.

38. (Withdrawn) The recombinant tissue protective cytokine of claim 37, wherein a said acetylated cytokine is comprised of alpha-N-acetylerthropoietin; N-epsilon-acetylerthropoietin; alpha-N-acetyl, N-epsilon-acetylerthropoietin; alpha-N-acetylasialoerythropoietin; N-epsilon-acetylasialoerythropoietin; alpha-N-acetyl, N-epsilon-acetylasialoerythropoietin; alpha-N-acetylhyposialoerythropoietin; N-epsilon-acetylhyposialoerythropoietin; and alpha-N-acetyl, N-epsilon-acetylhyposialoerythropoietin.

39. (Withdrawn) The recombinant tissue protective cytokine of claim 35, wherein a lysine residue of said cytokine is succinylated.

40. (Withdrawn) The recombinant tissue protective cytokine of claim 39, wherein said succinylated cytokine is comprised of alpha-N-succinylerythropoietin; N-epsilon-succinylerythropoietin; alpha-N-succinyl, N-epsilon-succinylerythropoietin; alpha-N-succinylasialoerythropoietin; N-epsilon-succinylasialoerythropoietin; alpha-N-succinyl, N-epsilon-succinylasialoerythropoietin; alpha-N-succinylhyposialoerythropoietin; N-epsilon-succinylhyposialoerythropoietin; and alpha-N-succinyl, N-epsilon-succinylhyposialoerythropoietin.

41. (Withdrawn) The recombinant tissue protective cytokine of claim 16, wherein said cytokine comprises at least one lysine residue modified by 2, 4, 6 trinitrobenzenesulfonate sodium or another salt thereof.
42. (Withdrawn) The recombinant tissue protective cytokine of claim 16, wherein said cytokine comprises at least one nitrated or iodinated tyrosine residue.
43. (Withdrawn) The recombinant tissue protective cytokine of claim 16, wherein said cytokine comprises an aspartic acid or glutamic acid residue that is reacted with a carbodiimide followed by reaction with an amine.
44. (Withdrawn) The recombinant tissue protective cytokine of claim 16, wherein a said amine is glycineamide.
45. (Withdrawn) An isolated nucleic acid molecule that comprises a nucleotide sequence which encodes a polypeptide comprising the recombinant tissue protective cytokine of any one of claims 1, 2, 3, 4, 5, or 6.
46. (Withdrawn) A vector comprising a nucleic acid molecule of claim 45.
47. (Withdrawn) An expression vector comprising a nucleic acid molecule of claim 45 and at least one regulatory region operably linked to the nucleic acid molecule.
48. (Withdrawn) The vector of claim 46 or 47 that is a pCiNeo vector.
49. (Withdrawn) A genetically-engineered cell which comprises a nucleic acid molecule of claim 45.
50. (Withdrawn) A cell comprising the expression vector of claim 45.
51. (Withdrawn) A pharmaceutical composition comprising a recombinant tissue protective cytokine of any one of claims 1, 2, 3, 4, 5, or 6, lacking at least one activity selected from the group consisting of increasing hematocrit, vasoactive action,

hyperactivating platelets, pro-coagulant activities and increasing production of thrombocytes, the cytokine having at least one responsive cellular protective activity selected from the group consisting of protecting, maintaining, enhancing or restoring the function or viability of a responsive mammalian cell, tissue or organ.

52. (Withdrawn) The pharmaceutical composition of claim 51, formulated for oral, intranasal, or parenteral administration.

53. (Withdrawn) The pharmaceutical composition of claim 51, formulated as a perfusate solution.

54. (Currently amended) A method for protecting, maintaining or enhancing the viability of a responsive cell, a tissue comprising a responsive cell, or an organ comprising a responsive cell, wherein said cell, tissue or organ is isolated from a mammalian body, comprising exposing said cell, tissue or organ to an effective amount of a pharmaceutical composition comprising a mutein recombinant tissue protective cytokine, wherein said mutein recombinant tissue protective cytokine

(a) comprises the amino acid sequence of SEQ ID NO:10 with a substitution of an amino acid residue at one of more of the following positions:

(i) 11 to 15 [SEQ ID NO:1];

(ii) 44 to 51 [SEQ ID NO:2];

(iii) 100 to 108 [SEQ ID NO:3]; or

(iv) 146 to 151 [SEQ ID NO:4];

(b) has a reduced level of *in vivo* erythropoietic activity compared to native erythropoietin as determined by the exhypoxic polycythemic mouse bioassay; and

(c) has tissue protective activity *in vivo* as determined by the middle cerebral artery occlusion test or *in vitro* as determined by the P19 assay. , ~~wherein the viability of the cell, tissue, or organ is protected, maintained, or enhanced.~~

55. (Currently amended) The method of claim 54, wherein the mutein recombinant tissue protective cytokine ~~does not affect bone marrow~~ is nonerythropoietic.

56. (Currently amended) A The method of claim 54, wherein the mutein for protecting, maintaining or enhancing the viability of a responsive cell, a tissue comprising a responsive cell, or an organ comprising a responsive cell, isolated from a mammalian body comprising exposing said cell, tissue or organ to a pharmaceutical composition comprising a recombinant tissue protective cytokine of any one of claims 1, 2, 3, 4, 5, or 6, that lacks at least one activity selected from the group consisting of increasing hematocrit, vasoactive action, hyperactivating platelets, pro-coagulant activity and increasing production of thrombocytes, wherein the viability of the cell, tissue, or organ is protected, maintained, or enhanced.

57. (Currently amended) A method for ~~the~~ protecting against and or preventing a tissue injury ~~as well as or~~ restoring and or rejuvenating tissue and or tissue function in a mammal, comprising exposing said tissue to a an effective amount of a pharmaceutical composition comprising a mutein recombinant tissue protective cytokine of any one of claims 1, 2, 3, 4, 5, or 6, wherein said mutein recombinant tissue protective cytokine

(a) comprises the amino acid sequence of SEQ ID NO:10 with a substitution of an amino acid residue at one of more of the following positions:

(i) 11 to 15 [SEQ ID NO:1];

(ii) 44 to 51 [SEQ ID NO:2];

(iii) 100 to 108 [SEQ ID NO:3]; or

(iv) 146 to 151 [SEQ ID NO:4];

(b) has a reduced level of *in vivo* erythropoietic activity compared to native erythropoietin as determined by the exhypoxic polycythemic mouse bioassay; and

(c) has tissue protective activity *in vivo* as determined by the middle cerebral artery occlusion test or *in vitro* as determined by the P19 assay. ~~that lacks at least one activity selected from the group consisting of increasing hematocrit, vasoactive action, hyperactivating platelets, pro-coagulant activity and increasing production of thrombocytes, wherein the method results in protection against and prevention of a tissue injury as well as restoration and rejuvenation of tissue and tissue function in a mammal.~~

58. (Currently amended) The method of claim 57, wherein the mammal has or is at risk for cognitive dysfunction, a seizure disorder, chronic seizure disorder, epilepsy, convulsions, nerve root compression, myotonic dystrophy, muscular dystrophy, multiple sclerosis, stroke, hypotension, cardiac arrest, central nervous system injury, neuronal loss, ischemia, subdural hematoma, subarachnoid bleeds, aneurysm, aneurysmal bleeds, myocardial infarction, inflammation, age-related loss of cognitive function, radiation damage, chemotherapy damage, radiotherapy damage, whole brain irradiation damage, cerebral palsy, cerebral supranuclear palsy, progressive supranuclear palsy, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, Huntington's disease, Tourette's syndrome, Leigh disease, Guillain Barre, dementia, AIDS dementia, senile dementia, Lewy body dementia, memory loss, amyotrophic lateral sclerosis, alcoholism, a neuropsychiatric or neuropsychological disorder, mood disorder, anxiety disorder, anxiety, schizophrenia, schizoaffective disorder, obsessive-compulsive disorder, panic disorder, uni-polar affective disorder, depression, major depressive disorder, dysthymic disorder, mania, bi-polar affective disorder, attention deficit disorder, attention deficit hyperactivity disorder, autism, a prion disease, Creutzfeldt-Jakob ~~Creutzfeld-Jakob~~ disease, Friedrich's ataxia, Wilson's disease, trauma, concussive injury, brain or spinal cord trauma or ischemia, heart-lung bypass, neurological defects from heart-lung bypass, post-operative cognitive dysfunction, embolic injury, hypoxia, mitochondrial dysfunction, abdominal aortic surgery, heart injury, myocardium injury, heart trauma, chronic heart failure, eye tissue damage, macular degeneration, diabetic neuropathy, diabetic retinopathy, glaucoma, retinal ischemia, ~~or~~ retinal trauma, retinitis pigmentosa, optic nerve damage, retinal detachment, arteriosclerotic retinopathy, hypertensive retinopathy, retinal artery blockage, retinal vein blockage, hypotension, a condition associated with hypoglycemia or diabetes, diabetes mellitus, nephrotic symptoms, acute renal failure, or hepatitis.

59. (Withdrawn) A method for facilitating the transcytosis of a molecule across an endothelial cell barrier in a mammal comprising administration to said mammal a composition comprising said molecule in association with a recombinant tissue protective cytokine of any one of claims 1, 2, 3, 4, 5, or 6, lacking at least one activity selected from the group consisting of increasing hematocrit, increasing blood pressure, hyperactivating platelets, and increasing production of thrombocytes.

60. (Withdrawn) The method of claim 59, wherein said association is a labile covalent bond, a stable covalent bond, or a non-covalent association with a binding site for said molecule.

61. (Withdrawn) The method of claim 59, wherein said endothelial cell barrier is selected from the group consisting of the blood-brain barrier, the blood-eye barrier, the blood-testis barrier, the blood-ovary barrier, the blood-heart barrier, the blood-kidney barrier, and the blood-placenta barrier.

62. (Withdrawn) The method of claim 59, wherein said molecule is a receptor agonist or antagonist hormone, a neurotrophic factor, an antimicrobial agent, an antiviral agent, a radiopharmaceutical, an antisense oligonucleotide, an antibody, an immunosuppressant, a dye, a marker, or an anti-cancer drug.

63. (Withdrawn) A composition for transporting a molecule via transcytosis across an endothelial cell barrier comprising said molecule in association with a recombinant tissue protective cytokine, of any one of claims 1, 2, 3, 4, 5, or 6, lacking at least one activity selected from the group consisting of increasing hematocrit, vasoactive action, hyperactivating platelets, pro-coagulant activity and increasing production of thrombocytes.

64. (Withdrawn) The composition of claim 63, wherein said association is a labile covalent bond, a stable covalent bond, or a non-covalent association with a binding site for said molecule.

65. (Withdrawn) The composition of claim 63, wherein said molecule is a receptor agonist or antagonist hormone, a neurotrophic factor, an antimicrobial agent, a radiopharmaceutical, an antisense oligonucleotide, an antibody, an immunosuppressant, a dye, a marker, or an anti-cancer drug.

66. (Withdrawn) Use of an recombinant tissue protective cytokine of any one of claims 1, 2, 3, 4, 5, or 6, lacking at least one activity selected from the group consisting of increasing

hematocrit, vasoactive action, hyperactivating platelets, pro-coagulant activities and increasing production of thrombocytes.

67. (Withdrawn) The use of claim 66, wherein said association is a labile covalent bond, a stable covalent bond, or a non-covalent association with a binding site for said molecule.

68. (Withdrawn) The use of claim 66, wherein said molecule is a receptor agonist or antagonist hormone, a neurotrophic factor, an antimicrobial agent, a radiopharmaceutical, an antisense oligonucleotide, an antibody, an immunosuppressant, a dye, or a marker, or an anti-cancer drug.

69. (Currently amended) The method of claim 57, wherein the mutein recombinant tissue protective cytokine is administered to the mammal prior to a surgical procedure.

70. (Previously presented) The method of claim 69, wherein the surgical procedure is cardiopulmonary bypass surgery.

71. (New) A method for protecting, maintaining or enhancing the viability of a responsive cell, a tissue comprising a responsive cell, or an organ comprising a responsive cell, wherein said cell, tissue or organ is isolated from a mammalian body, comprising exposing said cell, tissue or organ to an effective amount of a pharmaceutical composition comprising a mutein recombinant tissue protective cytokine, wherein said mutein recombinant tissue protective cytokine

- (a) comprises an amino acid sequence comprising amino acid positions 1 to 10, 16 to 43, 52 to 99, 109 to 145, and 152 to 166 of SEQ ID NO:10;
- (b) has a reduced level of *in vivo* erythropoietic activity compared to native erythropoietin as determined by the exhypoxic polycythemic mouse bioassay; and
- (c) has tissue protective activity *in vivo* as determined by the middle cerebral artery occlusion test or *in vitro* as determined by the P19 assay.

72. (New) A method for protecting against or preventing a tissue injury or restoring or rejuvenating tissue or tissue function in a mammal comprising exposing said tissue to an effective amount of a pharmaceutical composition comprising a mutein recombinant tissue protective cytokine, wherein said mutein recombinant tissue protective cytokine

- (a) comprises an amino acid sequence comprising amino acid positions 1 to 10, 16 to 43, 52 to 99, 109 to 145, and 152 to 166 of SEQ ID NO:10;
- (b) has a reduced level of *in vivo* erythropoietic activity compared to native erythropoietin as determined by the exhypoxic polycythemic mouse bioassay; and
- (c) has tissue protective activity *in vivo* as determined by the middle cerebral artery occlusion test or *in vitro* as determined by the P19 assay.

73. (New) The method of claim 72, wherein the mammal has or is at risk for cognitive dysfunction, a seizure disorder, chronic seizure disorder, epilepsy, convulsions, nerve root compression, myotonic dystrophy, muscular dystrophy, multiple sclerosis, stroke, hypotension, cardiac arrest, central nervous system injury, neuronal loss, ischemia, subdural hematoma, subarachnoid bleeds, aneurysm, aneurysmal bleeds, myocardial infarction, inflammation, age-related loss of cognitive function, radiation damage, chemotherapy damage, radiotherapy damage, whole brain irradiation damage, cerebral palsy, cerebral supranuclear palsy, progressive supranuclear palsy, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, Huntington's disease, Tourette's syndrome, Leigh disease, Guillain Barre, dementia, AIDS dementia, senile dementia, Lewy body dementia, memory loss, amyotrophic lateral sclerosis, alcoholism, a neuropsychiatric or neuropsychological disorder, mood disorder, anxiety disorder, anxiety, schizophrenia, schizoaffective disorder, obsessive-compulsive disorder, panic disorder, uni-polar affective disorder, depression, major depressive disorder, dysthymic disorder, mania, bi-polar affective disorder, attention deficit disorder, attention deficit hyperactivity disorder, autism, a prion disease, Creutzfeldt-Jakob disease, Friedrich's ataxia, Wilson's disease, trauma, concussive injury, brain or spinal cord trauma or ischemia, heart-lung bypass, neurological defects from heart-lung bypass, post-operative cognitive dysfunction, embolic injury, hypoxia, mitochondrial dysfunction,

abdominal aortic surgery, heart injury, myocardium injury, heart trauma, chronic heart failure, eye tissue damage, macular degeneration, diabetic neuropathy, diabetic retinopathy, glaucoma, retinal ischemia, retinal trauma, retinitis pigmentosa, optic nerve damage, retinal detachment, arteriosclerotic retinopathy, hypertensive retinopathy, retinal artery blockage, retinal vein blockage, hypotension, a condition associated with hypoglycemia or diabetes, diabetes mellitus, nephrotic symptoms, acute renal failure, or hepatitis.